UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
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ENDO PHARMACEUTICALS, INC.
and GRUNENTHAL GMBH,

Plaintiffs,

v. 12 Cv. 8060 (TPG)

TEVA PHARMACEUTICALS USA, INC.,
and BARR LABORATORIES, INC.,

Defendants.

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New York, N.Y.
March 26, 2015
12:00 p.m.

Before:

HON. THOMAS P. GRIESA

District Judge

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(Trial resumed)

THE COURT: I am deeply apologetic to keep this courtroom full of people waiting, but it was totally unavoidable.

So you go ahead, please.

MR. SABHARWAL: Thank you, your Honor.

For the record, your Honor, Keeto Sabharwal, on behalf of Amneal Pharmaceuticals, representing the defendants.

Before we begin, your Honor, I just wanted to make sure that your Honor has the David Lee white witness binder in front of the court as well as our cross-examination binder --

THE COURT: I have the big white binder.

MR. SABHARWAL: -- that is black in color, your Honor, with a blue highlight on top of it. It says "Amneal Pharmaceuticals."

DAVID LEE, previously sworn.

CROSS EXAMINATION (continued)

BY MR. SABHARWAL:

Q. Good morning, Mr. Lee. How are you this morning?

A. I am very good, thank you.

Q. Dr. Lee, you have been very patient. I am going to try to move through this quickly. As I said, the issues that we are going to be talking about really don't overlap with what Mr. Weiss was talking about.

Just a couple of housekeeping items before we get into

the substance. I wanted to make sure that the record was very clear about the specific exhibits we were talking about yesterday.

If you could please turn, sir, in the black binder to tab 6. Tell me when you are there, please, sir.

A. Yes, I am.

Q. And that is, for the record, Plaintiffs' Exhibit 0589, correct?

A. It is, yes.

Q. And that is the August 20, 2000, meeting minutes, correct, sir?

A. August 21, I believe, yes.

Q. August 21, yes. Great. Okay.

Directing your attention to the tab 4 in your black binder, are you there, sir?

A. I am, yes.

Q. That is the Plaintiffs' Exhibit 345, the September 14, 2000, project team meeting minutes, correct, sir?

A. That's correct.

Q. Two more.

Tab 8 in your black binder, that is the -- can you please read the exhibit number there? I want to make sure it is --

A. I have Exhibit DTX 2977.

Q. Great. Thank you.

And then the last one is in tab 7 of your binder. Could you read the exhibit number for that, sir?

A. Certainly. That is DTX 2974.

Q. Very good. Thank you, sir. All right.

I would now like to direct your attention, Dr. Lee, to PTX 0588, which is tab 5 in your black binder.

THE COURT: Which tab again?

MR. SABHARWAL: Your Honor, that would be tab five in the black binder, PTX 0588.

Q. Are you there, sir?

A. I am, yes.

Q. This appears to be another Alliance Committee meeting minutes, correct, sir?

A. That is correct, yes.

Q. The date is October 26, 2000, correct?

A. That's correct, yes.

Q. And it looks like, among other people, you and Dr. Baichwal attended the meeting?

A. Yes, that's correct.

Q. There were a number of issues discussed. One of them was the manufacturing process to Novartis which had been completed, correct?

A. Correct, yes.

Q. Then directing your attention to the next page, you see where it says patent update, sir?

A. Yes, I do, on page 4 of those minutes.
Q. I believe it says "A. Baichwal presented a summary of the discussions that had taken place with the patent attorneys. A draft patent application will be available shortly."
Do you see that, sir?
A. I do.
Q. Do you recall ever seeing this draft patent application, sir?
A. I don't recall. I'm not sure which draft patent application is being referred to here.
Q. Okay. And do you recall attending this meeting with the patent attorneys? Just a "yes" or "no" answer.
A. I don't, no.
Q. Thank you. Down below there is something about licensing opportunities. Do you see that, sir?
A. I do.
Q. It appears that a joint team had visited UPSA. Do you see?
A. I do, yes.
Q. What is UPSA?
A. I don't know what the initials UPSA stand for, but I think it was a European subsidiary of the Bristol-Meyers Squibb Company.
Q. The second sentence says UPSA has contacted Endo and indicated they are interested in Opana ER, correct?
A. Correct.

Q. The indication was for noncancer pain?
A. It actually says an indication for noncancer pain --
Q. -- is key for them, yeah.
A. So it wasn't just that indication.
Q. And do you recall what happened with this meeting between Endo and UPSA?
A. I have actually some very vague recollections of the meeting, which I think took place in Paris, but the eventual outcome, there was never an agreement, final agreement signed with UPSA.
Q. Okay. Great. Thank you very much.

I would like to direct your attention to PTX 144 that is in your white binder.

A. Okay, I have that.
Q. Sir, this, again, appears to be another Alliance Committee meeting minutes.

THE COURT: Where are we now?

MR. SABHARWAL: I am sorry, your Honor. We are at PTX 0144, and I am on the first page.

THE COURT: All right.

BY MR. SABHARWAL:
Q. I would like to scroll down, and do you see there is a section there that says "key discussion points"?
A. I do.
Q. In one of those key discussion points, it says, "Timing of

final report for study EN3202-15, study report will be finalized by 5/15/01 following resolution of several QA issues," correct?

A. Yes, that's correct.

Q. "QA" is "quality assurance"?

A. Quality assurance, yes.

Q. It was confirmed that the preliminary study results and conclusions would not change as a result of the resolution of the QA issues, correct?

A. That is also in here, yes.

Q. Did you have involvement in that decision, sir?

A. Yes, I'm sure I did, as a member of that team.

Q. Thank you.

There are a number of pages in here that appear to be a Power Point, if you go toward the end of the document, and I am going to direct you now to 792. It is a black page, and I will give you the full numbers. It is ENDO_OP_0171792. Do you see that, sir?

A. No. Just give me a moment, please.

Q. Please take your time.

A. Okay.

Q. Am I correct that this particular presentation was given at the May 2, 2001, Alliance Committee meeting?

A. That is correct.

Q. Directing your attention to the next page, which is now --

and I am reading the bottom page number, and it looks like this has been produced twice -- ENDO_OP_0171799. Do you see that?
A. I do.
Q. It looks like this particular document relates to study 15 final report, right?
A. That's correct.
Q. Can you read the conclusion in the third bullet point.
A. It says, "Results/conclusions don't change. Resolution ensures questions not raised by agency."
Q. When you say "results/conclusions," that's the results of study 15, right?
A. That was the preliminary results of study 15. That's what it has been referred to here.
Q. And the resolution ensures questions not raised by the agency. That's the FDA, correct?
A. The word "agency" refers to the Food and Drug Administration.
Q. That's not the patent office, correct?
A. That's correct.
Q. Thank you, sir.

We are moving pretty quickly. I am now going to move to a different topic.

Do you recall, sir, during your testimony...

(Pause)

MR. SABHARWAL: Your Honor? I was just waiting. May

I continue, sir?

THE COURT: Have you got a question pending?

MR. SABHARWAL: Your Honor, I saw that you had asked a question. I wanted to wait until your Honor was ready.

THE COURT: Well, as long as we are paused, what I would like to ask you to do, at a time when it makes sense to you, is to really do what I have asked other lawyers to do, and that is to tell me what it is you are presenting.

MR. SABHARWAL: Of course.

THE COURT: Because I hear the details, but I am not sure that I completely understand what -- where you are going. At a time when it is convenient for you, why, discuss that with me.

MR. SABHARWAL: I certainly will, your Honor. Would the court like me to do that right now?

THE COURT: Fine.

MR. SABHARWAL: Your Honor, first of all, just as a way of identifying myself, whenever I am standing up, it is more than likely that I am going to be talking about the on-sale bar issue, which is one of the other defenses that we have in this case, not the obviousness issue in terms of the direct evidence that we are going to be doing.

So the on-sale bar issue, your Honor, has two components that we have to prove before a certain date. One of them is that the claims that are being asserted against the

defendants are ready for patenting, were ready for patenting before what we call the critical date. In order for us to do that, your Honor, we have to show what was being discussed and we have to show what were the admissions that were being made about the claims and where they were in terms of their knowledge of the product prior to the critical date which in this case is October 15, 2000.

One of the things that's happened --

THE COURT: October 15, 2000, is a year before --

MR. SABHARWAL: -- the filing of what's called the provisional application, your Honor. We can try to put it up if we have it.

Can we put up that opening slide?

THE COURT: If you could do that again. I think you have shown it before.

MR. SABHARWAL: It is right in front of you, your Honor.

THE COURT: Good.

MR. SABHARWAL: Would you like me to walk you through it, your Honor?

THE COURT: It would help.

MR. SABHARWAL: Okay. Under the patent law, your Honor, you have a year from the time that you essentially recognize the facets of your invention that is defined by the claims. So the effective filing date, the actual date that is

not in dispute here is that Endo filed their application on October 15, 2001. If they had filed their application based upon that, they have a year grace period.

THE COURT: Say that again.

MR. SABHARWAL: Sure. There is a year grace period that you have. So if I come and I come up with an invention, your Honor, I have a year grace period before I either put it into the public domain or I offer it for sale. That's the bottom line. What we are trying to show here is that all of the activities that were necessary to meet both the "offer for sale" component as well as the "ready for patenting" component occurred before October 15 of 2000.

Because it did not fall within that time period between October 15, 2000, and October 15, 2001, we will demonstrate by clear and convincing evidence that all of the claims of both '122 and '216 are invalid based upon the on-sale bar. It is essentially a strict liability. If there is a finding of these two things, it is a pretty simple issue; and then the court can either say, yes, your evidence shows that you met this or, no, and that's it.

THE COURT: Look. I thought I understood this. Looking at this chart now, I really don't entirely understand it. So go over this again if you would.

MR. SABHARWAL: Of course, your Honor.

So, your Honor, do you see the date August 21, 2000?

THE COURT: Yes.

MR. SABHARWAL: That was a document that I just spoke with Dr. Lee about in which they had made a decision to proceed with NDA approval because Dr. Lee admitted that they had already completed the necessary studies to show that their product was efficacious. And, as Mr. Black said, efficacy over a 12-hour period is the most important thing in the invention, and we have an admission from Dr. Lee about that based upon a written document.

And, just to be fair, I'm sure that Mr. Black has a different version, and I am sure that we will have a debate about, this a professional debate.

So these other things, your Honor, frankly are not germane necessarily to Dr. Lee. Dr. Palmieri, our expert, will be taking the court through each of these step by step to show that the dissolution studies had been completed, the formulation had been completed, the pharmacokinetic studies that are referenced in the claims had been completed, and the analgesic studies had been completed and they had gotten to a point where they were going out, getting licensing partners, they were getting patent applications, and they did not ultimately file their application in a timely fashion.

And the law is very clear. You only get a year from the time that you make this recognition. I think that the parties are going to have some debate about this. We don't

have that many witnesses that we are going to be cross-examining. Unfortunately for Dr. Lee, he is one of them

THE COURT: You are just going to have to do a little repetition.

MR. SABHARWAL: Of course.

THE COURT: Again, what is meant by the critical date?

MR. SABHARWAL: Sure. The critical date is the date, whenever you see that, your Honor, you can say, okay, that's the defendants' date. The defendants have to show me that everything that they need to prove the on-sale bar occurred before that. We have to get to the left of that red sign.

The plaintiff, I suspect, is going to say, no, they didn't do that. There are a number of things that are to the right of that sign.

So if we prove everything to the left --

THE COURT: Let me interrupt you. Of course the significance of that year, what is that?

MR. SABHARWAL: Because under the statute, your Honor, 35 U.S.C. 102(b), the law says that you cannot put something on sale or in public use more than a year before your filing date. And in this case the filing date is October 15 of 2001.

THE COURT: Say that once more, please.

MR. SABHARWAL: Of course. Of course. You see that filing date there, your Honor, October 15 of 2001?

THE COURT: Yes, I do.

MR. SABHARWAL: You have a year, if you go backwards, you have a year from the time that you have completed what you need to file a patent, all right? So if the plaintiffs can show that the activities that led to the invention, not for the FDA, but for the patent office, occurred between October 15 and 2001, then they can argue that we have not met --

THE COURT: This date occurred when?

MR. SABHARWAL: Between October 15, 2000, and October '1. What we are arguing is hey Endo had everything --

THE COURT: You mean October 15, 2001?

MR. SABHARWAL: Yes, your Honor.

THE COURT: Say that again, then.

MR. SABHARWAL: Of course.

THE COURT: I think that was a little confusing.

MR. SABHARWAL: I think that was my fault.

THE COURT: Say it again.

MR. SABHARWAL: Of course.

Under the patent law you have a year from the time that you file your provisional to file your patent application. From the time that you recognize you have either put something on sale and it is ready for patenting, you have one year. Maybe the easier way to look at this, because it is a little bit confusing, you see this date August 21, 2000, your Honor, up in the blue?

THE COURT: Yes, I do.

MR. SABHARWAL: Our contention is going to be that no later than this date, or perhaps September, by that time, Endo had all of the information it needed to file the application and they had already engaged a company to start commercial manufacturing. They were already collecting inventory. They were buying product from Novartis. And, based upon that, under the law, they had one year from that time to get a patent on file with the patent office. They did not do that. That's the bottom line.

THE COURT: Let's see if I understand.

MR. SABHARWAL: Sure.

THE COURT: In other words, there comes a time when, for various reasons, a party has everything needed to file for a patent.

MR. SABHARWAL: Yes.

THE COURT: Now, that time is X, let's say.

MR. SABHARWAL: X.

THE COURT: Now, they don't have to file for the patent on ten days after X, but they have to file for the patent no later than a year from X, is that right?

MR. SABHARWAL: That is exactly right, your Honor.

THE COURT: And your contention is, again? You have said it many times. Say it again.

MR. SABHARWAL: My contention is, very simply, they missed the date. My contention is, our contention is, based

upon Endo's own documents and some of the admissions that we got yesterday and some of the other evidence that we are going to see, that they had all the information they needed to file this patent application. They were speaking with patent attorneys in July. But, for whatever reason, it didn't happen.

I am not in any way, your Honor, to be clear, accusing Endo of anything nefarious or fraudulent. We don't have to do that, and I am not doing it. I am just saying that, under the strict liability on-sale bar, you have a grace period of one year from the time that you recognize your invention and you have to get it on file. It is like anything else in any other facet of the law.

THE COURT: I will be back to you, Mr. Black, but just another few questions for this same lawyer.

MR. SABHARWAL: Sabharwal.

THE COURT: Sabharwal.

If everything necessary for filing for a patent occurred, let's say, by November 2000, then they would be okay, right?

MR. SABHARWAL: If -- there is no evidence -- if we fail to show that they knew or should have known that they filed -- they had everything ready to file until November, then we have not proven our case, that is correct.

THE COURT: But what you say is you believe you have proved that everything was set for the filing of the patent

before October 15, 2000, and that's your case, right?

MR. SABHARWAL: That is part of our case, your Honor.

The other part of our case is what is called the offer for sale. We have to show that there was a commercial offer for sale here. In other words, under the law, if there was a transaction between a supplier and Endo, and we can show that with documents and testimony, then we have met the -- and that occurred also before October 15 of 2000, if we show the court that and we show the court the ready for patenting and the court concludes, yeah, I see that both of those things occurred before that date, then all of the claims that are asserted against all of the defendants will be invalid pursuant to 35 U.S.C. 102(b), as opposed to what Mr. Weiss was talking about, which was obviousness under 103.

May I proceed?

THE COURT: Let me hear from Mr. Black.

MR. SABHARWAL: Mr. Black, do you want to come back here.

MR. BLACK: Actually, I would.

I will be brief.

We largely agree with the defendants on the law, your Honor, but there are two requirements. There is the "on sale" requirement and the "ready for patent" requirement. And the way the law came about is, let's say I invented this water bottle today and I thought this was a great idea and I went out

and sold this water bottle to the public and shipped it all around the country, and then two years later I said to myself, I forgot to get a patent, I would really like to get a patent and a monopoly. I can't do that. In the United States, at least during the relevant time period, you could sell for six months and then go and file your patent. As long as you were within a year after you started selling, you were okay under the law. Does that make sense?

THE COURT: Yes, I understand.

MR. BLACK: On the other hand, if you invented something and kept it secret forever, then this bar doesn't apply. The penalty applies if you sell the product and then later try to go get the patent.

THE COURT: Okay.

MR. BLACK: So they have to show two things: one, that the inventions described in the claims -- and they have to go one by one through the claims -- were ready for patenting at the time, and we have already led the evidence that showed that the clinical studies, which are discussed in the patent and which were necessary to prove that this would work for 12 hour relief, were not done anything -- they were done a couple of weeks before the patent was filed, not more than a year.

So we disagree on whether it was ready for patenting. That's a factual issue your Honor will have to decide. They do bear the burden on that by clear and convincing evidence,

though. It is not a 50/50 thing. It is clear and convincing.

The second part is, they have to show there was a sale. We haven't heard much about it yet, but the sales they are relying on are not sales by Endo to the public, because it is undisputed that we didn't sell any products. We didn't even get FDA approval until 2006. So they have got a kind of creative theory that Endo's contracting with a supplier to provide tablets, under a servicing agreement to make the tablets for Endo, triggers the on-sale bar. And, again, your Honor will have to decide that. They are saying we obtained tablets from somebody. Endo is small. They got somebody else to make the tablets for the clinical trials and for the development work and they are saying that, by having somebody else make the tablets, this bar was triggered.

THE COURT: Okay. Thank you very much. Okay. Let's resume.

MR. SABHARWAL: Does that cover it, your Honor?

THE COURT: Yes.

MR. SABHARWAL: Very good. Thank you.

So, your Honor, just in terms of an interim statement, what we are now going to be turning to are these clinical trials that are part of the dispute on the ready for patenting that Mr. Black says were after 2000 and I said he didn't need them, okay?

THE COURT: Fine.

BY MR. SABHARWAL:

Q. When did you testify, sir, on your direct? I'm losing track of the days. Tuesday, right?

A. I began on Tuesday.

Q. Began on Tuesday. Your direct was on Tuesday. And you testified regarding a study, regarding study 3202-009, right?

A. I believe so, yes.

Q. And that is the steady state study?

A. That is the study that is known as the steady state study, yes.

Q. I would like to direct your attention to, in your white binder -- white binder, your Honor -- 281. Tell me when you are there, sir.

A. I am there.

THE COURT: Wait a minute.

MR. SABHARWAL: No problem, your Honor. Tell us when you are ready.

THE COURT: 281, I have it.

MR. SABHARWAL: It's going to be a pretty easy question, your Honor.

Q. Okay. Now, according to this document -- I am on Plaintiffs' Exhibit 0281, looks like page 1, it looks like this study -- the steady state study was initiated on October 25, 2000, right?

A. Yes, that is correct.

Q. And it was completed on November 22, 2000, correct?
A. That means that it was completed in the clinic on November 22, 2000.
Q. In the clinic. Okay. And then you had a report date it looks like August 14 of 2001, right?
A. That is correct.
Q. You would agree with me, sir, that this study hadn't even started before Endo and Penwest were -- strike the question.

You would agree with me that Endo hadn't even started this study, study 9, before Endo had reached a "go" decision with respect to analgesic efficacy as set forth in the August and September 2000 meeting minutes, isn't that correct?
A. That.

THE COURT: That was a long --

MR. SABHARWAL: A long question.

THE COURT: Hard for me to follow. Can you break that down, please?

MR. SABHARWAL: Absolutely. Let's get everything together and then we can take a look at it because I am a little confused by it.

This is going to be my tab 5. What tab is it for Dr. Lee? Tab 6.
Q. Go to tab 6 in the black binder.

MR. SABHARWAL: Your Honor, in the black binder, tab 6. And for the record this is PTX 589.

Q. Tell me when you are there, sir.
A. Yes, I am there.
Q. This says, there are those three "go/no go" questions that we talked about yesterday. Do you remember?
A. Yes, I do.
Q. The ones you were involved in designing, right?
A. Correct, yes.
Q. And the date here is August 21 of 2000, right?
A. That's correct, yes.
Q. This was before you started the steady state study, is that correct?
A. It was before the study began in the clinic, yes.
Q. And then remember we talked about a September press release as well for meeting minutes? What tab is that, Dr. Lee?
MR. SABHARWAL: That would be tab 4, your Honor; tab 4, Dr. Lee. And that is Plaintiffs' Exhibit 345.
THE COURT: Tab 4.
MR. SABHARWAL: In your black binder, your Honor.
THE COURT: Okay.
Q. Are you there, sir?
A. I am, yes.
Q. You would agree with me that the designation of status completed for both the sustained release dosage form and the go decision number two efficacy had been completed also prior to starting the steady state study, isn't that correct?

A. Yes these studies were done for the investment decision, yes, and were completed by this time, or at least we had preliminary results from them.
Q. When you say investment decision, what do you mean?
A. The decision that I think is referred to in the press release that you mentioned yesterday --
Q. I see.
A. -- which said, Penwest actually said, we are prepared now to invest in a full scale clinical program that will take this to hopefully an NDA, an approved NDA.
Q. So you were ready to go commercial then, right?
A. We weren't ready to go commercial.
Q. Were you ready to engage in a commercial activity at that point, to start filing FDA, an NDA?
A. You have to clarify. I'm sorry.
Q. Sure. You said this was an investment decision. In other words, you made these decisions. You issued these press releases. You are now going forward with the NDA, right?
A. No, that is not correct.
Q. That's what it says here.
A. Where? When you say "here," where do you mean?
Q. You say, "Determination of efficacy. Is this product an analgesic at tolerated doses? If yes, proceed to NDA --
THE COURT: A little slower.
MR. SABHARWAL: I'm sorry, your Honor.

Your Honor, I am on clinical program status.

THE COURT: I see that.

MR. SABHARWAL: Okay.

Q. So tell me if I am reading this correctly Dr. Lee. It says, "If yes, proceed to NDA filing as rapidly as possible. Status completed." Right?

A. With all due respect, counsel, I think you are misrepresenting what is written here. When it says, "If yes, proceed to NDA filing as rapidly as possible," you are implying that all of the work necessary to file an NDA had been complete.

MR. SABHARWAL: No, no, no, I am absolutely not saying that. I'm sorry. If that was what I was implying -- I have read the documents, sir. I am certainly not saying that.

I am saying that you embark on the filing of the NDA. You did not -- you had not completed the studies for purposes of a completed NDA package.

A. We hadn't even started many of the studies.

Q. And for purpose of the NDA, I am not contesting that you had completed them, so I apologize. Okay.

Now, you looked at the patent claims, right?

A. Yes, I have.

Q. With respect to the '122 patent, those patent claims that have been asserted against defendants don't have any steady state limitations, do they?

A. I am not sure about that actually. I absolutely should --
Q. Let's take a look. I am now going to direct your attention to PTX 001. That is tab 1 in your black binder.
MR. SABHARWAL: Your Honor, if you could please turn to PTX tab 1, the words that we are looking for, your Honor, are "steady state" in the claims.
THE COURT: Okay. I am at tab 1 in the black binder, which is the patent.
MR. SABHARWAL: Your Honor, could you please turn to the claims which are going to be towards the back.
Q. Dr. Lee, let's give the court a second to get there. Would you like me to repeat the question, sir?
A. Yes, please.
Q. My question is --
THE COURT: Just a second.
MR. SABHARWAL: Sure.
THE COURT: Column what?
MR. SABHARWAL: Column 25.
THE COURT: Give me a minute to get there. Okay.
Q. Do you see the words "steady state" -- I am never going to be able to say that -- "steady state" in claim one, sir?
A. I don't.
Q. Do you see "steady state" --
THE COURT: Where is the word "steady state"?
MR. SABHARWAL: They are not there, your Honor.

That's what I am trying to establish.

THE COURT: Okay.

Q. Now directing your attention to claim 2, the words "steady state" are not there either, right?

A. That's correct.

Q. And they are not in claim 3 either, correct?

A. That's correct.

Q. And not in 19 either, correct?

A. Those words are not there.

Q. And those words are not in claim 20 either, correct?

THE COURT: What words are you talking about?

MR. SABHARWAL: The words "steady state," your Honor.

Q. You were saying, sir?

A. The words "steady state" are not in claim 20.

Q. Thank you.

THE COURT: What's the significance of this?

MR. SABHARWAL: The significance of this, your Honor, is there may be an argument, I think there will be an argument that the claimed inventions rely on a steady state condition, and the steady state study was not completed until after the critical date, therefore, there will be an argument by Endo that we did not meet our burden. And we just established that there is no steady state limitation in the claims. Mr. Black said that we need to show the invention in the claims. There is no steady state limitation in those claims. I'm sure that

on redirect we will probably hear something different. I just wanted that clarified for the record.

THE COURT: All right. I understand.

BY MR. SABHARWAL:

Q. If we can now move to the '216 patent, maybe I can shortcut this for you, sir. Are you aware that there are no steady state limitations in any of the claims asserted against the defendants in the '216 patent?

A. I, without reading through these claims, wouldn't like to --

Q. Very fair. Very fair.

MR. SABHARWAL: This would be tab 2 in your black binder, your Honor, tab 2 in your black binder.

THE COURT: Right. I am there.

MR. SABHARWAL: And now the tab in my binder, I have no idea. 2. Okay. Good. That's easy.

Q. There are a lot of claims here, sir. I am not going to take you through every one.

A. Great.

Q. Just 46 of them.

So if you could turn to column 26, your Honor, that's where we are going to start. It may be easier if you skim through this and let me know if you see the words "steady state" in any of the claims.

MR. BLACK: Your Honor, I think the patent is in the

record. It would take --

THE COURT: Keep sitting down.

MR. BLACK: I'm sorry. The patent is in the record and whether the words "steady state" appear or do not appear in any of the claims is something we can all agree on or not agree on later. To have the witness read through it seems --

THE COURT: Keep seated. I am not hearing you.

MR. BLACK: Your Honor, he is about to have the witness read through each of the claims in the patent to determine whether the words "steady state" appear in the claims. That seems time wasting, because the patent is in the record and we can all look for ourselves whether it is there or not later.

MR. SABHARWAL: Your Honor, may I respond?

THE COURT: Go on with your questions. You are doing okay.

MR. SABHARWAL: Thank you, your Honor. This will just take a minute.

BY MR. SABHARWAL:

Q. Do you see the words "steady state" in any of the claims of the '216 patent?

A. In a quick glance through the H2 claims, I don't see the words "steady state."

Q. And I will represent to you that they are not in there and I also represent to you that if I find them I will let you

know.
A. Thank you.
Q. Moving right along, you testified yesterday regarding the Opana clinical development plan, right?
A. Correct.
Q. You remember we saw a slide with a whole bunch of clinical trials on it?
A. I do.
Q. I believe it was 33?
A. Something like that, yes.
Q. And would you agree with me that not all 33 were necessary in your opinion to get a patent, correct?
A. That's correct.
Q. And we had actually talked about certain studies that you believed were in the patent, right? For example, the steady state study?
A. Correct.
Q. I would like to now hear about a study 8. Were you familiar with that study, sir?
MR. SABHARWAL: That is, by the way, in your white binder. That is PTX 0279, your Honor, PTX 0279.
THE COURT: Where is that?
MR. SABHARWAL: PTX 0279.
THE COURT: How do I locate that.
MR. SABHARWAL: It is in the white binder. I don't

think there are tabs in plaintiffs' binder.

MR. BLACK: There are. Maybe we gave you one without tabs.

MR. SABHARWAL: Okay. Thank you.

Mr. Black --

THE COURT: Are you referring to this binder?

MR. SABHARWAL: Yes, we are.

THE COURT: Where?

MR. SABHARWAL: May we approach? I can find it easier.

THE COURT: Sure.

Q. Are you there, sir?

A. Yes, I am.

MR. SABHARWAL: Are you there, your Honor?

THE COURT: Yes.

BY MR. SABHARWAL:

Q. Okay. I believe you testified that the primary -- let me start over.

You did testify about this study, right?

A. I am not sure about that. You maybe have to remind me of that.

Q. In an abundance of caution, let's take a look at it.

For the record, this is just an excerpt that is in your binder, right.

A. That's correct, yes.

Q. And this was a study that was initiated, according to this, on May 2001 and completed on June 19, 2001. Did I see that correctly?

A. That is completed in the clinic --

Q. Yes.

A. -- in June 2001.

Q. In other words, the CMO, or whatever, had completed the clinical studies by that time?

THE COURT: By what time?

MR. SABHARWAL: I am trying to get that from the witness, your Honor.

THE WITNESS: So, your Honor, by June 19, 2001, the volunteers had completed their participation in this study.

THE COURT: I see that date. All right. Fine.

BY MR. SABHARWAL:

Q. Sir, in one of the documents that were produced to us, we saw a description of the study date which said that it was to further investigate the effect of food on the bioavailability of oxymorphone?

THE COURT: Where are you reading now.

MR. SABHARWAL: Your Honor, this document is not in the binder. I will read it into the record. It will show up on your screen. It is ENDO_OP_0179037.

THE COURT: What is this?

Q. Have you seen this document before, sir?

A. I'm sure I have. I don't immediately recollect it, but I am sure I have.
Q. Okay. If you flip to the second page here, I have a full copy here can I hand it to you.
MR. BLACK: We have a logistical problem here, which is that the agreement was that cross documents would all be in the binder so we could have them, and this one is not in the binder nor has a DTX label. So can we get a copy of it?
MR. SABHARWAL: Sure.
MR. BLACK: And I would appreciate it if counsel, when doing cross, would put all of the documents in the binder, as we agreed.
MR. SABHARWAL: Mr. Black, this actually just came up at the last minute.
MR. BLACK: You could have sent it to me last night, Mr. Sabharwal, but you decided not to. Your behavior is consistent.
MR. SABHARWAL: That's unfortunate. I guess maybe you were busy crossing the witness who was still on cross.
BY MR. SABHARWAL:
Q. Do you have the document, sir?
A. I do, yes.
Q. Directing your attention to the second page, it says, "Effect of meal type and timing on the viability of oxymorphone following administration of oxymorphone CR."

Do you see that?

A. Yes, I do, yes.

Q. On the left side, it says "EN3202-008." Do you see that?

A. I do.

Q. Here is what I want to ask. It says, "The primary purpose of this study is to further investigate the effect of food on the bioavailability of oxymorphone. Both meal type and timing of the dose relative to the meal will be studied."

Do you see that?

A. I do.

Q. But hadn't you already done this type of study with respect to EN3202-003 which is meant to investigate the effect of food on bioavailability with a high fat meal?

A. This was a higher unit dose of Opana ER, so these were 40 milligram tablets and we were required to ensure that the highest unit dose of Opana ER that we were planning at that time behaved in the same way as earlier lower doses that we had tested.

Q. And that was the FDA that required it?

A. I think it was both the FDA and us internally requiring it. I think we needed to know how our product was performing.

Q. Right. But was it a specific request by FDA to do this study along with your internal discussions?

A. I don't know that it was a specific request, but the Food and Drug Administration, we assume, will require that you

evaluate the highest unit dose of the product you are developing.

Q. Okay. Thank you very much. You can put that aside, sir.

You also testified on Tuesday regarding EN3202-12, and I think this may be my last study. Do you recall that study, sir?

A. I do.

Q. I believe that during your direct testimony you showed a slide as to where you said the study 12 relates to in the '122 patent. I can show you that slide.

A. Yes, please do.

Q. Of course. If you don't have a hard copy in front of you, you can use mine, but I am going to put it up on the screen. This would be slide 44. Can we put that up, please? Do you see it, sir?

A. I do, yes.

Q. And on the left side you agree with me that's the '122 patent, right?

A. It is, yes.

Q. On the right side is a copy of the cover page of the study 12, correct?

A. That's correct.

Q. It was your testimony a few days ago that the data for the figures that's recited here came from study 12, is that right?

A. That's right.

Q. So here is where I get a little confused. If we look at figure 1, can we pull figure 1 of the patent up? Actually let's go to slide 46. That will be easier. Sir, in your demo -- would you agree with me that these are slides from the '122 patent figures 1 to 4?

A. Yes, I would.

Q. On the left side, the left vertical axis is measuring pain intensity through one of the pain intensity indicators I learned a few days ago, VAS?

A. That's correct, yes.

Q. As opposed to something like TOTPAR?

A. For instance, yes.

Q. Or SPID.

A. That's another one.

Q. I learned a lot over the last couple of days.

So the only parameter that is being measured on the left side is the VAS specific parameter regarding pain intensity difference, right?

A. It's not the only one, because there is also categorical pain scale, which is also shown in the slide.

Q. Okay. Fair enough, categorical pain. And that's at the bottom, right?

A. That's at the bottom, yes.

Q. On the horizontal axis is time, right?

A. Yes.

Q. And then can you explain to me what is on the right vertical axis?
A. That is the pain scale, as you have indicated there, visual analog scale that we have shown earlier.
Q. Isn't this the plasma concentrations?
A. I'm sorry. I apologize. I am looking at the wrong side. Yes.
Q. No problem.
A. You are absolutely correct. It is the plasma concentrations of oxymorphone and 6-hydroxy-oxymorphone.
Q. Again, just to clarify for the court, on the left side we have VAS vertical. On the right vertical we have the concentration of 6-OH-oxymorphone, for example, in the first top left, and then on the horizontal we have time, right?
A. That's correct, yes.
Q. And I believe you testified that you were trying to show the correlation between pain intensity and the amount or concentration of 6-OH-oxymorphone, is that correct?
A. Oxymorphone and 6-OH-oxymorphone, yes.
Q. In fact, in the patent, in the section that you pointed us to, there is a particular paragraph, can we blow that up? So this is from column five, sir. This says, as can be seen from these figures, 1 to 4, "There is a correlation between pain relief and both oxymorphone and 6-hydroxy-oxymorphone levels." Do you see that?

A. Yes.
Q. And I assume you agree with that statement?
A. Yes.
Q. Then it says, "As the blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone increase, pain decreases." Do you see that?
A. Yes.
Q. And do you agree with that?
A. Yes.
Q. "Thus, to the patient, it is the level of oxymorphone and 6-hydroxy-oxymorphone in the blood plasma which is 'most important.'" Do you see that?
A. Yes.
Q. And you agree with that?
A. Yes.
Q. My first question is, are you sure that the data that you are relying on came from study 12?
A. The data that is described here came from two different studies.
Q. So not just study 12?
A. The pain data came from study 12. The blood level later came from a different study.
Q. And what study was that, sir? Because you didn't mention that the other day.
A. I'm not sure I was asked about that the other day.

Q. Okay. I can read your testimony, but that's okay.
A. The blood level data came from one of the other studies, and I would have to refresh my memory as to exactly which study it was.
Q. Okay. No problem. But just let's look at your testimony, because maybe I misunderstood. I thought you said that -- I thought you testified that figures 1 to 4 in the patent come from study 12. Was that not correct?
A. Well, if I didn't say specifically that the pain data came from study 12, the blood level data, and I think it is actually indicated in the patent, it nowhere says that the blood level data and the pain data came from the same study. I don't believe it does, anyway.
Q. I think that's not what you said, but I just want to make the record clear.

MR. SABHARWAL: Can we pull up transcript 209/line 22 to 210/line 4. Okay. It is really difficult to read. Here we go.

Q. 209/22: "There are two other studies that I want to mention" -- this is Mr. Black -- "what was the status of study 12?

"At the time of this May 2001 meeting, the study had been completed in the clinic, so all of the patients who were intended to be treated had been treated, and no more patients were being enrolled," and it goes on. Right?

A. Right.
Q. I don't know if this is the right one. Let's go to 213. So we have now introduced the study. Go to 213/line 11. Okay here we go:
"Yes, it is in the patent. It is in the patent known as the '122, in column 5, and the patent at lines 9 to 43, you said the VAS score was taken based upon asking patients how much pain they were in. Could you tell us what that is on slide 45?"
So I want to be clear, because maybe it was my confusion, that only some of the data in figures 1 to 4 came from study 12, right?
A. The pain data in figures 1 to 4 came from study 12.
Q. But the concentration of the oxymorphone came from a study, and you just don't remember what study it was.
A. It did not come from study 12. It came from one of the pharmacokinetic studies, and I would have to -- I wouldn't want to give you misidentified study numbers and confuse the situation.
Q. No problem. Now, I am almost done.
Now, isn't it true, sir, that it has never been established that there is a correlation between the concentration of oxymorphone and the pain relief that it provides?
A. If you are saying -- well, perhaps I shouldn't put words in

your mouth. Perhaps you could just clarify what you mean there, because obviously we have shown some relationship between blood levels and pain relief, but perhaps you can explain further what you mean.

Q. What I mean is by a prior deposition of yours in which you were asked that question and I believe you said there is no correlation. That's why I am confused.

A. Well, I can't remember exactly what I say, whether I said there is no correlation or no correlation had been proven to the satisfaction of the of the FDA.

THE COURT: We will take our lunch until 2:15.

MR. SABHARWAL: Lunch until 2:15? Yes, sir, your Honor.

(Luncheon recess)

AFTERNOON SESSION

(2:15 p.m.)

THE COURT: Go ahead, please.

MR. SABHARWAL: Thank you, your Honor.

BY MR. SABHARWAL:

Q. Dr. Lee, good afternoon.

A. Good afternoon.

Q. I only have a few more questions. I would like to go back to the subject that we were talking about right before the lunch, and that was the Figures 1 to 4 in the patent. Do you recall that?

A. I do, yes.

Q. And there was a certain section in Column 5 I was asking you about the correlation between the blood plasma level and pain relief. Do you recall that?

A. I do, yes.

Q. Can we pull that up, please.

For the record, Dr. Lee, I am in the '122 patent that is in your white binder columns 31 to 40 something. Column 35 to 42 or something like that. It's hard to read on my screen.

Tell me when you're there.

A. Can you -- sorry, I'm trying to find it in my hard copy, can you --

Q. I can come over and show it to you but Column 5.

A. Sorry, I have gone too far.

Q. Column 5 I think maybe the 31, beginning with the words, "As can be seen from these figures?"
A. Right.
Q. And it's actually on your screen as well.
A. It's fuzzy on the screen, but I can see it.
Q. Same here. I have to take my glasses off here.
But we talked about this before, right?
A. We did, yes.
Q. And you said that you agree with the statement, for example, in the middle of paragraph beginning at line 35: Thus, to patient it is the level of oxymorphone and 6-hydroxy-morphone in the blood plasma which is most important, correct?
A. That's what is written here.
Q. In other words, as the blood plasma level of oxymorphone increases, the pain decreases?
A. In general, yes, that's right.
Q. And the reason that I'm confused is I thought you said that you agreed with this statement.
A. I agree with the statement as is written here, yes.
Q. Okay. Now Dr. Lee, do you recall that you were previously deposed in this case in September of 2009?
A. I do, yes.
Q. And at that time -- just for the record it's a prior case, you were representing Endo in 2009?

A. Okay, yes.
Q. And you were deposed in that case, correct?
A. I was, yes.
Q. And that testimony related to Opana ER, correct?
A. Yes, it did.
Q. Isn't it true, sir, that you were asked the following question:

Is there a correlation of Opana ER's pharmacokinetic properties to the pain relief that it provides?

And you responded: That's never been established.

Do you recall that?

A. I don't recall those specific words, but I'm sure what you're reading is correct, yes.
Q. And then you actually went on in that, and the question was asked:

So if --

MR. BLACK: Could we have the page and line number?

MR. SABHARWAL: Sure, I'm sorry. That is going to be page 108, starting line 7 -- actually starting line 3.

Q. And the question was asked: Why has that not been established?

And your answer was: With this class of molecule opioids, it is not proven to be so far or proven to be very difficult to establish a correlation between blood levels and analgesic effect.

Do you recall saying that?
A. I can recall that being discussed, yes.
Q. So here's why I'm confused, and maybe it's just me, why is it that you agree with the statement in the patent that there is a correlation, but you said under sworn testimony in 2009 that that has never been established?
A. It's, again, the context of it, and I totally don't remember the context in which the question was asked in 2009, but certainly the answer that I gave then, what I'm pretty sure I had in mind, is as far as the Food and Drug Administration was concerned, in other words, proving beyond a reasonable doubt that there is a correlation in which one studies and then does appropriate modeling in the same patient measuring both blood levels and pain relief, or in a group of patients, and then proving statistically beyond a reasonable doubt that there is a correlation, that is what I think I was referring to hadn't been done and was difficult to show.
Q. Let me see if I understand what you're saying. Even though you agree that your statements in your patent that there is a correlation between blood plasma and oxymorphone, you nevertheless said the opposite in your deposition, but that was based upon a proof beyond a reasonable doubt assumption?
A. Yeah, I'm not sure I would agree with you that they're the opposite. I think actually on the figures that you're referring to, there is actually a little R, and it says R

equals -- I forget exactly, I don't have it in front of me, which is in fact a statistical test.

Q. Okay.

A. And what was done there was attempting to show statistically, based upon the data that is presented in the patent and in which we have said came from two different studies, that there was a correlation between the lines on those charts.

What I believe, but it was in 2009 that I was referring to in the deposition, was is there proof that the Food and Drug Administration would accept that you could prove that there is a correlation between blood levels and pain relief in the same patient measured in the same study.

Q. Okay.

A. So I don't see a conflict there, but obviously that's open.

Q. I'm not here to debate with you, sir, but you would agree with me that to a lay person like me, if I'm reading where it says there is a correlation in the patent and then reading where you say that there has in fact never been established a correlation, that would create an apparent inconsistency, wouldn't you agree?

A. As you say, an apparent inconsistency.

Q. All right. But your position is because your testimony, which I believe was in a patent case, you were talking about in the context of the FDA?

A. Again, I don't remember the context of the question, but --
Q. Well, I don't see anything here where you're clarifying it that with respect to the lack of correlation that was with respect to the FDA. Do you recall at some point sending what we call an errata sheet on this deposition to say that well, my testimony was really from the viewpoint of FDA?
A. I don't recall sending such an errata sheet.
Q. Because again, this says the question was: So if Opana ER delivers oxymorphone over a twelve-hour period, this doesn't necessarily indicate that the patient will receive pain relief for twelve hours, is that correct?

You said: That's correct.

Then the question was: How much pain relief will a patient get from one dose of Opana ER?

Your answer was: Highly dependent on each individual patient.

Question: So you cannot tell how much pain relief a patient will get from one dose of Opana ER?

Answer from you: That's correct, it's not possible to predict that.

Now here's where I get confused -- So far you agree that you said that, or do you want me to show you the transcript?
A. Let's leave it for the moment I agree with what you just read there.

Q. So here's where I get confused, and this is in 2009, it says: So Endo has not made any claim of Opana ER's efficacy based solely on pharmacokinetic properties, is that right?

And you said: That's correct.

And that was in 2009, isn't that right, sir?

A. That's right.

Q. But isn't it true that your patent is making that type of correlation?

A. Well, you used the word "claim." It depends how you're using the word "claim" there. Sorry, I'm putting words in your mouth now, but I assume you're implying "claim" in the sense of a patent claim, whereas I'm sure in that question I was -- I had in my mind "claim" in the sense of a marketing claim.

Q. I see. Okay. So you certainly wouldn't say that with respect to any of the patent claims there's a correlation, right?

A. So in the patent, as I just mentioned, we have shown there is the charts there and there was a statistical evaluation done of the correlation between those lines between the pain relief and the plasma levels, and that shows some statistical correlation between those two lines.

Q. Right. But in your sworn testimony in 2009 after this had been filed you said that Endo has not made any claim of correlation between pain and pharmacokinetic parameters, isn't that true?

A. We're back to same thing I just said. I was talking there claim, or at least I had in my mind, maybe pain it wasn't clarified, claim in relation to a marketing claim, not a patent claim.
Q. But with a patent claim you would be comfortable making that assertion but you wouldn't be comfortable making that assertion in a marketing claim, is that what you're saying?
A. Marketing claims have to be approved by the Food and Drug Administration. And as I have said earlier, proving to the Food and Drug Administration's satisfaction that there is a correlation between blood levels and pain relief hasn't been shown. But that's different to -- we're using the word "claim" in two different contexts there.
Q. Did you ever tell FDA that you had actually made statements to the patent office that there is in fact a correlation -- a positive correlation between pain relief and the amount of drug?
A. I really can't answer that question, I have no idea.
Q. You don't know, and you don't know whether Endo ever let them know that, do you?
A. I have no idea, no.
Q. But in your mind, you were sort of separating what you were saying to the FDA versus what you were saying in the patent, right?
A. I have been encouraged to do that.

Q. And who encouraged you to do that?
A. Yourself. I mean we separate what we need to prove to the FDA, you want to keep the FDA out of this, and what is in the patent, so I'm just following with what you are saying.
Q. I'm saying you said you were encouraged to keep them separate. Who encouraged you?
A. I thought you were doing that.
Q. No, I wouldn't encourage you to do anything.
A. Then I misunderstood.
Q. Let's move on.

Sir, isn't it true that you actually told the FDA the opposite of what you told -- what you said in your patent application regarding the correlation between blood plasma and amount of pain?

THE COURT: What's the question again, please?

MR. SABHARWAL: Your Honor, the question that I'm asking the witness is whether or not the witness said the opposite to FDA as what he said in his patent.

MR. BLACK: Your Honor, this is the second day of cross of this witness --

THE COURT: Keep seated because I can't hear.

MR. BLACK: It's the second day of cross of the witness. This is argumentative. He's reading from a deposition where the witness was testifying about the FDA. He's conflating the word "claims." This is irrelevant.

MR. SABHARWAL: Your Honor, this is highly relevant. I think we have a situation here --

THE COURT: I'm going to overrule the objection. You go ahead. And the witness I'm sure will listen carefully, and if there's a need for clarifying, he will do that, and then there can be redirect.

MR. SABHARWAL: Thank you very much, your Honor.

BY MR. SABHARWAL:

Q. Dr. Lee, I want to be clear that I'm not accusing you of anything, I am just confused myself and I want to see if I can understand the testimony, okay, so the record clear?

A. Absolutely.

Q. So please don't take anything from the questions I'm asking you, but I do have to ask: Isn't it true that you told the FDA that there was actually a negative correlation between blood levels of 6-OH oxymorphone and pain relief?

A. If I ever told the FDA that, I certainly have no recollection.

THE COURT: Say it again, I didn't hear it.

MR. SABHARWAL: Sure, your Honor.

THE COURT: I'm not hearing the witness.

THE WITNESS: Sorry, your Honor. I said -- counsel asked me if I had made a particular statement to the Food and Drug Administration, and I was saying that I don't have any recollection of making such a statement.

Q. Okay. Now I'm going to hand you select pages of your NDA.

MR. SABHARWAL: I want to say for the record before anybody gets upset, this is purely for impeachment, and the reason we're bringing this out is because the witness does not recall making the statement. So I am going to hand up this document. It is a long document, I'm going to ask you about two pages.

THE COURT: I don't need any of that.

MR. SABHARWAL: Sorry, your Honor.

Q. Now Dr. Lee, you have been here for a long time and I am not going to ask you to read this whole thing.

A. Thank you.

Q. I would like you to confirm for the record that this is DTX 0962 and the title of this is Endo Pharamaceuticals oxymorphone extended release ER tablets application summary dated December 16, 2002.

Do you see that, sir?

A. I do, yes.

Q. And you recognize this as an FDA-related document, sir?

A. I do.

Q. Now I'm going to direct you to paragraph -- page 98, it will be on the screen. Hopefully this will be my last couple questions.

Tell me when you're there, sir.

A. Okay.

Q. Do you see where it says 6.10?
A. I do.
Q. Pharmacokinetic, pharmacodynamic relationships?
A. I do.
Q. I'm sorry, go ahead to the second paragraph.

The second paragraph, it says -- and this is a lot of language here, but you see the sentence it says "Analysis?"
A. Yes.
Q. It says: Analysis of the data, meaning the data for Opana ER, did not reveal a linear relationship between plasma oxymorphone concentrations and pain intensity. There was a weak but statistically significant association indicating that pain intensity increased as the concentration of 6-OH oxymorphone increases. This association is not in the expected direction and is the result of a few data points. These analyses were very limited in scale and should not be viewed as conclusive.

Do you see that, sir?
A. I do.
Q. Did you agree with that statement at the time it was sent to the FDA?
A. I'm sure I did.
Q. So here's my question, sir: Is there a positive correlation between blood plasma concentration of 6-OH oxymorphone pain relief, no correlation, or a negative

correlation? Because we have three different statements from three different documents, and now I'm very confused.

A. Well, based upon the data presented here and what is written here, it is not possible to say that there is any correlation or no correlation or some correlation. It says this association is not expected, it's the result of a few data points. The analyses were very limited in scale and should not be viewed as conclusive. In other words, there's no conclusion that could be drawn from these.

Q. Do you recall ever telling the FDA there is in fact a positive correlation between pain relief and blood plasma concentration of 6-OH oxymorphone?

A. What we told the FDA is contained in this document.

Q. That was not my question. My question was: Do you recall ever telling the FDA what you said in your patent, which is that there is a positive correlation between 6-OH oxymorphone or oxymorphone and pain relief? Yes or no.

A. No, I don't.

Q. Okay. And conversely, you never told the patent office that you told FDA that there is a negative correlation between pain relief and the level of oxymorphone, isn't that right?

A. There is no negative correlation.

Q. What is this saying? This is saying that actually as you increase --

THE COURT: Keep your voice up a little bit.

MR. SABHARWAL: Sorry, your Honor.

Q. Isn't it true, sir, this document is saying that the more oxymorphone you get, the higher your pain intensity?

A. It says it's the result of a few data points and should not be viewed as conclusive.

Q. I understand that.

A. Well, there is no negative correlation. It doesn't say that here.

Q. Well, did you ever tell the patent office that you testified that there has never been established any correlation between 6 oxymorphone and pain intensity in your sworn deposition in 2009?

A. I have never had such a discussion with the patent office.

Q. Do you know if anyone has ever bothered to tell the patent office that the senior executive of the company testified about a statement that is directly contrary --

THE COURT: That's just an argumentative question.

MR. SABHARWAL: I withdraw the question.

Q. Do you know whether anyone at Endo has informed the patent office about the testimony regarding no correlation between oxymorphone and pain intensity?

A. I don't know if anybody from Endo has ever said that.

MR. SABHARWAL: Thank you. I have no further questions at this time.

THE COURT: Does any other attorney have cross?

All right. Then let's go to redirect. Do you have redirect?

MR. BLACK: Yes, your Honor, may I have five minutes to consult with my team?

THE COURT: Of course you may.

MR. BLACK: Take a short break?

THE COURT: Take your time, but we won't take a break.

MR. BLACK: Okay.

(Pause)

REDIRECT EXAMINATION

BY MR. BLACK:

Q. Dr. Lee, would you take out your white witness binder and turn to patent PTX 1. If you would turn to the -- open the page to column 25 where the claims begin. There were a series of questions about Claim One and whether or not the words "sustained release" appears in the claim. Do you recall that?

A. I do, yes.

Q. I'm sorry, let me get my place here.

If you would look over to the left side of the page in column 23.

A. Yes.

Q. In particular at line 6 there's a statement there, "The intent of a controlled release opioid," would you read that into the record?

A. The intent of a controlled release opioid formulation is

the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a steady state where continued administration will produce the same results when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a steady state test and may require periodic administration over an extended time period, ranging from several days to a week or more.

Q. Thank you, that's good.

So the words "steady state" does not appear in the claim, but we see it several times in the discussion of the intended use of the product, correct?

A. Correct.

Q. Would you turn in your binder to PDX 217. Do you recall some questions about the size of the pain market?

A. I do.

Q. Would you take a look at the page that is marked Endo OP 0360378.

A. Okay.

Q. And do you see that it says market dynamics?

A. I do.

Q. What's the first word?

A. Unsatisfied.

Q. Do you recall why that was written?

A. Because at the time we believed that there was still very significant under-treatment of moderate to severe chronic pain. Literally tens of millions of Americans suffer from long-term chronic, moderate to severe pain, and the drugs that were available to treat them were just inadequate or not adequate enough, I should say, perhaps I should clarify.

Q. Please turn to PTX 157 also in your white binder.

A. Okay.

Q. These are the meeting minutes of the project team meeting held on January 22nd, 1998.

A. Correct.

Q. And there were some questions about dissolution curve.

Before we get there, please turn to Endo OP 0126499. And can you tell us what we see here?

A. Yes, this is a table in fact of so-called stability data in which several different experimental formulations of Opana ER were tested in standard stability tests. And these are the results of those standard stability tests again for several different experimental formulations.

Q. Had formulation been selected at this point?

A. No, it had not.

Q. And then on the next page, there's the curve that you spent some time on during cross-examination. Do you see that?

A. I do.

Q. And that refers to TIMERx V, what is TIMERx V, if you know?

A. TIMERx V, that is one of the grades of TIMERx, the matrix that was the basis of Opana ER's formulation. But this particular grade of TIMERx, which I think was evaluated in experimental formulations in the laboratory, never progressed any further.

Q. Yesterday you noted that the dissolution curve shown to you for this prototype formulation did not indicate the testing conditions used to generate the dissolution curve. Why was that important?

A. There are several different methodologies and conditions under which dissolution can be tested in the laboratory. And I am far from certain that one can compare the results of one test with another unless the methodology, the equipment used and the medium, the conditions under which the tests are done, are explained and likely comparable. Otherwise, the results may not be comparable.

Q. Please turn back to PTX 1, the patent, and turn to table four, which is in column ten.

A. Okay.

Q. How many examples are shown in table four?

A. Three different formulation examples.

Q. And are those all formulations according to patent?

A. They are.

Q. At the time of the patent application filing, did you have a belief that all of these would work?

A. Yes, we did.

MR. BLACK: Let's put up slide 83 from the opening. And we'll identify the opening as PX 4003, your Honor, if that's okay.

THE COURT: Certainly.

Q. I'm going to represent to you that we have graphed here the dissolution curves or the three samples in the patent in gray. It's a little bit washed out on the screen, but I hope you can see it.

A. I can, yes.

Q. And the two red lines on either side, the bands are reflect the ranges in the patent. Do you see that?

A. I do, yes.

Q. Is it true that in the pharmaceutical industry dissolution testing -- it's common to use dissolution testing and for there to be a range of acceptable values around the curve that has been demonstrated to provide efficacy and that will also be expected to have similar efficacies?

MR. WEISS: Objection, leading.

THE COURT: Overruled.

A. Yes, that is standard in the pharmaceutical industry. Dissolution testing is the standard test that is done before batches of commercialized material are allowed out and allowed into the marketplace. So dissolution testing is an important component of the pharmaceutical industry's practices.

Q. Is it true or false that with dissolution testing it is common for there to be a range of acceptable values around a curve that has been demonstrated to provide efficacy that would also be expected to have similar efficacy?
A. Yes, that is true.
Q. Was it your responsibility to determine the appropriate values for the dissolution ranges in the patent?
A. No, that was not my direct responsibility.
Q. And you, in your cross-examination, said that you were not an expert in this area. What did you mean by that?
A. The individual who will define ranges, such as indicated here for instance by the red lines, would be somebody skilled in the art of formulation development. That is not my expertise.
Q. Would you take a look at Exhibit 157, PTX 157, also in your white binder.
A. Yes.
Q. Was the development work that led to Opana ER in the patents done by this point in time, which is February of '98?
A. No, it wasn't.
Q. Had you established that the product was fit for its intended purpose of twelve-hour pain relief yet?
A. No, we hadn't.
Q. Please take a look at Exhibit 589. And now we have to move to the black binder, I guess there may be two up there, black

binder with blue cover. Tab 6 in the black binder with the white and blue cover. It says Lee cross-examination exhibits.

A. Tab 6?

Q. Yes.

A. Right.

Q. You provided some testimony about the comments from C. Laudadio who presented preliminary results. Do you see that in the middle of the page?

A. I do.

Q. And under that are listed five studies, correct?

A. Correct.

Q. Including study twelve?

A. That's correct.

Q. Would you turn the page and read into the record the status of study twelve?

A. Yes, under the heading EN, a study EN3202-012, it says enrollment is ongoing and slightly behind schedule. Last patient to enroll is expected on 9/29 with database lock targeted for 10/16. Final study report is due by 12/19/2000.

Q. So there was an implication on cross that study twelve was done and supported a finding that there were preliminary results. Was that the state of affairs at that time?

A. No, the study was not completed. It was still ongoing, and there could not have been any results discussed or presented at this meeting, only the status of the study.

Q. Just for the record, can you describe the process of doing a study from -- just generally when is a study designed, enrollment of patients, the locking of database, can you describe that?

A. Yes. Very briefly, the study begins with the development of a study protocol, which describes all the steps that are going to take place in the study, including the type of patients to be enrolled and the number of patients to be enrolled. And it also describes the statistical plan, the plan, the method of statistical analysis, and the way in which the data will be handled once the study is completed.

Once the study protocol is approved, study sites are recruited, that is, clinical sites where there are doctors that specialize in conducting clinical trials and who see the type of patient that the study protocol requires. And there may be several sites around the United States that are enrolled in such a study. And the each study investigator is given a target number of suitable patients to enroll under that study protocol.

Over the next period of time, which could be days, weeks, months or even years, depending on the type of study, the study investigator will enroll the patients, treat them, and evaluate them according to the details laid out in the study protocol.

Q. What's a database lock?

A. When the study has been fully completed, and the target number of patients and the data collected from each of the study sites, and is brought to place where the data are going to be analyzed, there are individuals who are required to go through all of the data that is collected to make sure that it appears to be intact and there are no discrepancies or inconsistencies in the data.

And this is all done while the study is blind, in other words, nobody knows which of the patients received what of the active drugs in the study or the sugar pills, the placebo. Once all the data have been cleaned to the satisfaction of the chief statistician of the study and no further changes can then be made to the study data, the database is then locked. And at that point, nothing can be done to change any of the data unless there are some very special requirements met.

Q. And is it possible to run correlations or do anything with the data before the lock?

A. Yes, it may be possible to do that, but in what's known as a blinded fashion. So the data is divided up into perhaps groups A, B and C, and maybe some things could be done -- analyses, I shouldn't say "things," could be done, but that would be for a very specific purpose and wouldn't give you any specific information because you wouldn't know what those groups A, B and C, for example, are.

Q. With respect to study 15, turning back to the document, the bottom of the page, there's a note that says the database has been locked with final study report due October 30. Do you see that?
A. I do.
Q. Did the final study report arrive on October 30?
A. I don't believe it did, no.
Q. Why was it delayed?
A. There were some questions, some issues raised around this study, both in terms of its execution and in some elements of the statistical analysis.
Q. What was the problem in execution?
A. There was at least one study site where the study coordinator had been found to be diverting study drug for her own use and for the use of her friends. And at that point, it was decided that the data collected by that particular site was not reliable, and a decision was made to remove that data from the final analysis of the study.
Q. You were asked whether it was a goal of your development project to increase the oral bioavailability of oxymorphone with your formulation. Do you recall that?
A. I do.
Q. Did you do a test to compare oral bioavailability in solution versus in the controlled release formulation?
A. Yes, we did.

Q. And what was the result of that study?
A. We found that formulating oxymorphone in the formulation that became Opana ER did not have a negative impact or in fact a positive impact on the bioavailability of oxymorphone. It really didn't change the bioavailability significantly.
Q. That was surprising or not surprising?
A. We found that actually to be a rather pleasant surprise, yes.
MR. BLACK: Thank you, your Honor, let me confer with my team for a moment.
(Pause)
MR. BLACK: Thank you, your Honor, that's all I have on redirect.
MR. WEISS: May I your Honor, ask three or four questions to clarify the record on recross?
THE COURT: Sure, of course.
MR. WEISS: Thank you, your Honor.
RECROSS EXAMINATION
BY MR. WEISS:
Q. Dr. Lee, Mr. Black asked you to the effect of if it was your responsibility to define the ranges around the dissolution curves and you said it was not, correct?
A. It was not my direct responsibility, that's correct.
Q. Whose responsibility was it, please?
A. Formulators, formulation scientists.

Q. Can you tell me the name of the person?
A. I believe in this case it would have been Dr. Danny Kao or Dr. Danny Kao with members of his team.
Q. Do you know if he actually did that, or you're surmising?
A. He was the senior formulator on the project, and he is a named inventor, so I think it's a reasonable surmise.
Q. That he determined the ranges for the patent as opposed to the ranges that were required for tolerance on the commercial product?
A. Perhaps both, but I would be speculating then.
Q. And you explained for Mr. Black the requirements to do a database lock before analyzing the study, do you recall that?
A. I do, yes.
Q. That's a requirement of the FDA, right?
A. Well, it is a requirement of the FDA, but it's also good clinical practice, and no pharmaceutical company will conduct a clinical trial other than in accordance with good clinical practice.
Q. And you're not aware of a requirement to do a database lock before analyzing data for a patent, correct?
A. That is not something I have ever considered.
MR. WEISS: Thank you, your Honor.
Thank you again, Dr. Lee.
THE COURT: All right. Dr. Lee, thank you very much, and we'll have our next witness.

THE WITNESS: Thank you, your Honor.

MR. BLACK: Thank you, Dr. Lee.

We'll shuffle around a little bit. Mr. Rhoad will take command and move into the infringement case as the plaintiffs call Dr. Reza Fassihi.

MR. WEISS: If I could note, your Honor, also, the drawings that I worked on yesterday with Dr. Lee we have marked as DX 9000 for identification in the record, and we'll give a copy of that, of course, to everyone.

THE COURT: Are you offering that?

MR. WEISS: I think, your Honor, it's probably more formally a demonstrative. I just want the record to show what it was we did.

THE COURT: All right. You can have it marked for identification or received in evidence, whatever you wish to do.

MR. WEISS: If there's no objection, we would like to have it received in evidence so it's clear.

THE COURT: Received.

(Defendant's Exhibit 9000 received in evidence)

(Continued on next page)

REZA FASSIHI,

called as a witness by the Plaintiffs,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. RHOAD:

Q. Doctor, could you please state for the record your full name and where you live.

A. Reza Fassihi. I live in Fort Washington, Pennsylvania.

THE COURT: Could you spell your last name once again.

THE WITNESS: Fassihi, F-A-S-S-I-H-I.

Q. Have you prepared a set of slides to go along with your testimony here this morning?

A. Yes, I have.

Q. And where are you currently employed?

A. I'm employed at Temple University in Philadelphia.

Q. And what position do you hold there?

A. I am a professor of biopharmaceutics and industrial pharmacy.

Q. And can you tell the Court, please, what is biopharmaceutics?

A. Biopharmaceutics is that part of science that deals with drugs, solubility of the drug, absorption of drugs, dosage form design and all of that.

Q. And you said you were a professor of biopharmaceutics and industrial pharmacy. What is industrial pharmacy?

A. Industrial pharmacy is formulation development, preformulation, evaluation of the dosage forms both in vitro and also manufacturing of pharmaceutical dosage forms.
Q. And what are your responsibilities in your position as a professor of biopharmaceutics and industrial pharmacy at Temple?
A. Apart from some administrative responsibilities on the committees that I'm a member of many, my major role is to do teaching and research.
Q. And what is the nature of the research that you do?
A. My research focuses on development of dosage forms. I teach a number of graduate students that are in the program, and I teach various courses which relates to biopharmaceutics, pharmaceutical formulations, and so on.
Q. And to what extent does your research and teaching deal with oral control release dosage forms in particular?
A. I would say 80 percent of my research and teaching role is devoted to solid dosage forms.
Q. Can you tell us what type of work and what type of teaching you do relating to oral control release dosage forms?
A. In the school of pharmacy we have a large number of pharmacy students that graduate and become pharmacists. As part of their training they need to learn about dosage forms, pharmaceutical product, how they are developed, how they are evaluated, how they are approved by FDA. So I teach all of

that to my students.

For PhD side, the graduate students that go for PhD, we have courses that are more advanced. And they cover applied biopharmaceutics, which is application of biopharmaceutics, which I mentioned, that we apply to understand so the students can learn how drugs are absorbed, how they are evaluated as a dosage form, and also manufacturing. There are regulatory issues which relate to the development of dosage forms. I teach all of that.

Q. And have you done any consulting with the pharmaceutical industry, companies in the pharmaceutical industry relating to the design, development, and use of oral controlled release dosage forms?

A. Yes, I have.

Q. Can you summarize that for us?

A. Sure. I have consulted with many generic companies as well as brand companies. I have given seminars. I have given lectures. I have had collaboration in designing, developing, and progressing basically controlled dosage form throughout the processes, from very beginning to very end.

Q. And do you have any training or experience in consulting with doctors or other health care professionals regarding the proper use and administration of controlled release dosage forms?

A. Well, in the school of pharmacy, as professor of pharmacy,

I often -- of course I teach all about pharmacy, and my students will graduate, they will be doctor of pharmacy, they go to hospitals they go to private practices. But at Temple University and associated hospitals, whenever there is an issue with a pharmaceutical dosage form or physicians require information about a particular drug product, they call me. Many of them they know me, and if they don't, they will send an email and inquire about issues related to what the question is.

Q. And how about do you regularly consult with patients regarding a proper use and administration of prescription medications?

A. Patients -- my students who graduate and go as a pharmacy -- as a doctor of pharmacy out there, they deal with patients. And through those doctor of pharmacies I am also in contact with patients, but personally I'm not involved with patients.

Q. And can you describe for the Court your educational background, please?

A. I'm a pharmacist by training. I have bachelor's in pharmacy. I got my bachelor's back in 1974. I got a first class honors from Punjab University in India. I got my PhD, my doctorate in pharmaceutics from Brighton University in the United Kingdom.

Q. And what was the subject area of your doctoral research?

A. Major focus of my dissertation was solid dosage forms and

formulation development.
Q. And are you involved with or a member of any professional organizations relating to design, development, or use of controlled release formulations?
A. Well, I am a member of numerous societies. I am a member of the Controlled Release Society. I am a member of the American Association of Pharmaceutical Scientists. In fact, I'm a fellow of that organization. I am a member of the American Colleges of Pharmacy, and a number of other organizations.
Q. And have you been published in the area of oral controlled release formulations?
A. Yes, I have.
Q. Can you describe -- give a summary of the extent of your publications in that area.
A. Sure. I have published more than 130 peer reviewed publications. I would say 100 of them relate to control release dosage forms, how they work, how they are formulated, how they are evaluated. Those publications are all available on my CV.
Q. You mentioned your CV. Can you turn to PTX 794 in your binder and let us know if that is a copy of your CV, the larger white binder.
A. Sorry, you mentioned PTX?
Q. 794.

A. Maybe it is not in this binder. I found it, yes, it is, indeed. I'm sorry. Yes, it is my CV.

(Continued on next page)

Q. And does that CV provide more detail regarding your background and experience in these areas that you have been telling us about?
A. Yes, it does.
Q. Does that provide a more comprehensive listing of your publications in the area?
A. That's right, they are more in details and titles, journals where they were published, and so on.
MR. RHOAD: Your Honor, plaintiffs would offer Dr. Fassihi as an expert in the field of pharmaceutical sciences including, in particular, design, development, and use of oral controlled-release formulations.
THE COURT: All right.
Q. In connection with your work in this case, Dr. Fassihi, have you studied Endo's '122 and '216 patents?
A. Yes, I have.
Q. If you can turn in your binder, the large white binder, can you confirm that they are exhibits PTX 0001 and PTX 0005?
A. Yes, they are.
Q. Is it your understanding those are the two patents in suit that are at issue in this case with respect to the claims asserted by Endo?
A. Yes, I am.
Q. In connection with your work, have you also studied abbreviated new drug applications that have been filed by each

of the defendants in this case?
A. Yes, I have.
Q. Have you studied various portions of those abbreviated new drug applications?
A. Yes, I have.
Q. Is a common acronym for abbreviated new drug application "A-N-D-A"?
A. That's correct.
Q. Or ANDA?
A. ANDA, yes.
Q. As a result of the work you have done, have you formed any opinions as to whether the generic extended relief oxymorphone tablets described in each of the defendants ANDAs infringe claims of the two patents in suit, the '122 and the '216 patents?
A. Yes, I have.
Q. And what is your opinion?
A. After I have reviewed all the ANDA information and compared it with the patents, they do infringe the patents.
Q. And did you provide a series of reports in this case explaining in detail the basis for your opinions in that regard?
A. Yes, I have.
Q. Do those reports set forth your opinions and the bases for your conclusion that the defendants' tablets infringe the

patents in suit?
A. That's correct.
Q. Before we start getting into detail about your opinions in that regard, your Honor, I thought it would be helpful to give a background of the technology and some of the things that we have been talking about and that your Honor has been hearing about.

So maybe the first thing we could do, could you describe for the court exactly what an oral -- I mean an immediate release oral dosage form is?
A. Yes, as shown here on the screen, the immediate release dosage form releases substantially all of its drug within a short time frame, maybe, as you can see the animation, the tablet is swallowed and within a few minutes it disintegrates and everything gets absorbed.
Q. And is that, an immediate release oral dosage form, is that something that is compared to a controlled release oral dosage form?
A. If you move to the next slide, please, so controlled release dosage form releases a drug over a long time frame and rate of release is important and where drug is released in the human body. So the animation, you see the tablet swallowed and then some releases in the stomach; the dosage form moves inside the intestine and continuously releases the drug; and it reaches eventually the point where there is no more drug to

come out.

Q. Are there advantages to controlled release dosage forms as compared to immediate release dosage forms?

A. Of course. If you move to the next slide, please.

THE COURT: Keep your voice up a little more.

THE WITNESS: Sure. I get closer to the microphone.

A. Controlled release dosage forms, when they are administered, they are administered once a day, maybe twice daily. They are much more convenient and less disruptive to the patients. So patients, for example, at night, if you are sleeping, they don't have to wake up and take a tablet. They also improve patient compliance, and they also provide steadier blood levels, which is also very important to relieve pain. And the therapeutic effect is much longer than immediate release dosage forms.

Q. Can you describe for the court the way controlled release dosage forms work?

A. Sure. If you would move to the next slide, please. I believe I have divided how controlled release works into four step.

First, drug must be released from the dosage form; and then it should be absorbed into bodily tissues; and then it has to pass through the liver to get into bloodstream; and once in the bloodstream, it will be delivered to where the site of action is.

Q. Let's walk through each of those steps in a little more detail. Can you explain to the court what it means for the drug to be released from the dosage form and how that works?

A. Would you please turn to the next slide.

So release of drug from the dosage form, as I showed in the animation, once the drug is swallowed by the patient or even *in vitro* the drug has to be released first and then it has to be absorbed in order to be therapeutically effective. Rate of release is very critical in absorption process. Because if it comes out too fast, then it will be like immediate release, but it has to come out slowly. And the rate is also affected by everything which is in the GI tract, for example, solubility of the drug plays a role, the type of controlled release delivery system and formulation specifics and also interaction that is happening in the GI tract between food, nutrients, pH, everything else that is in the GI tract with the dosage form, all of that will impact release from the dosage form.

THE COURT: Can you just pause and let me read that, please.

THE WITNESS: Sure.

(Pause)

THE COURT: Okay. Go ahead.

A. So that was the step one that the drug is released.

If you move to the next slide, please.

Q. Could you talk to us about an example of one type of

controlled release dosage form and the way it operates?
A. Sure. One type of controlled release systems are referred to as matrix systems, and a matrix system is dosage form that can hydrate and swell. And I have one schematic here to show you, for example, in zero time there is tablet, and two hours it is hydrated and it is gelled.
Q. Can you explain to us exactly what's shown on these the zero hours?
A. Sure. In the zero hour it is just a plain tablet which is now placed in the aqueous environment. In two hours we see the tablet, and around the tablet there is a gel formation and still tablet is there. In four hours we can see that completely is now converted into a gel. Next, please. So here, at eight hours, gel has expanded and all of this is happening while the drug comes out. And go further, please. At 12 hours you can see that the dosage form is all now degraded and everything is released and dosage form is basically nonexistent.
Q. So this is just one type of controlled release dosage form. There are other types of oral released dosage forms, is that correct?
A. That's right, yes.
Q. But they all must first, as part of the first step, they must release the drug?
A. That is right. All of the controlled release dosage forms,

they have to release in a controlled manner.

Q. So let's move on to the next step, then. Can you describe the second step in a little more detail for us?

THE COURT: Before we do that, let's take a recess.

(Recess).

MR. RHOAD: Your Honor, to orient ourselves here, Dr. Fassihi was in the middle of explaining the four steps that a controlled release dosage product must go through typically to become effective. We have gone through the first step, the release of the drug out of the dosage form and into the gastrointestinal tract, either the stomach or intestines, and we are going to move on now to the second step in that process.

THE COURT: All right.

Q. Dr. Fassihi, could you please explain to the court the second step in the process by which controlled release dosage forms typically work?

A. Please, if you would go to next slide. So the second step is about absorption of drug into bodily tissues. So we talked about the fact that drug has to be released from dosage form and be absorbed to be therapeutically effective. It is first absorbed into bodily tissues, then we said that presence of food would impact how release is happening, how dosage form passes through the GI tract and physical/chemical properties of the drug, such as molecular weight, permeability, the stability in the GI tract, all of that will impact absorption.

So if you move to the next slide, please, so this is a tablet which releases drug --

Q. Just so the court is clear, you are now moving on to the third step in the process. It has been released from the dosage form, it has been absorbed into the bodily tissues, and now we are moving on to the third step, is that right?

A. That is correct, yes.

So drug is now released in the GI tract and, as I have shown here on this slide, it gets into bodily tissues which are epithelial cells. It goes into a major vein called portal vein.

Q. Can you point out for the court where exactly it is?

A. Sure, sure. On all the three red paths that lead into portal vein to the left-hand side of the slide, we can see that, and portal vein goes into the liver. In the liver, part of the drug is metabolized, and after that drug molecules going into bloodstream, as it is shown, on the upper part of the liver.

Q. Now, you said that in the liver the drug is metabolized. What do you mean by the term "metabolized"?

A. Every drug that goes through the liver, depending what type of drug it is, portion of that would be subjected to enzymes which are present, so -- thank you for the slide -- so enzymes in the liver can break down the drug. That is called metabolism. Extent of metabolism of course depends on

different drugs behave differently.

The rate of delivery of the drug to the liver also has something to do with the metabolism. For example, if everything is poured into liver, it can saturate the enzyme and more of drug goes into blood circulation. When it goes slower, the chances for greater metabolism is always there.

Q. A term that has been discussed some in this case before you took the stand is a term "bioavailability." Can you explain to the court what that term is?

A. If you would move to the next slide, please. So we talked about drug metabolism and here bioavailability, so on the right-hand side I have this schematic which represents, for example, if we give a drug, a dosage form which has 100 milligram of the drug in it, the blue color on the right-hand side, if, for example, 60 milligram of that 100 milligram is absorbed, we say it has bioavailability of about 60 percent.

Q. You are saying 60 milligrams gets absorbed?

A. Into the bloodstream.

Q. Into the bloodstream.

A. That's correct.

And the orange example is, again, another drug which has 100 milligram as an example in the dosage form and when it is swallowed by the patient and drug is released, what gets into blood circulation is only 10 percent of 100 milligram, that is 10 milligram, one-tenth. So in this case we say

bioavailability is 10 percent.

So basically the definition which I have put on the left-hand side of the slide "bioavailability" measures how much of the administered drug gets past the liver and becomes available in the body. And those were the examples which I have shown.

Q. And is one of the reasons why a drug would have a bioavailability that is less than 100 because of this metabolization or the metabolism that occurs in the liver?

A. That is correct, that is correct. So every drug has different percent bioavailability. Some drugs, like the orange one, whatever it is, it has bioavailability of 10 percent. The other one has bioavailability which is 60 percent. And this generally happens. But if you give something IV, for example, we introduce 100 milligram into blood circulation, so that is yardstick against which we can measure.

Q. So now we have covered the release of the drug from the dosage form, the absorption into the bodily tissues, the passage through the liver and the bloodstream. What's the next step, the fourth step in the process?

A. Yes, if you go to the next slide, please, once the drug pass the liver and it is now in the blood circulation, it reaches the site of action, and that is the therapeutic effect is observed at this stage.

Q. Let's return for just a moment to the first step in the

process, the release of the drug or the dissolution of the drug out of the dosage form, and talk about some of the things and some of the equipment that the judge has heard a little bit about already.

So if you can first tell us, is there a test that formulators use to measure this first step, to measure how much of the drug is released from the dosage form?

A. Yes. When we develop dosage form, we evaluate *in vitro*, see how much drug is released. If you go to the next slide please, the way we measure is referred to as dissolution testing.

Q. It refers at the top to *in vitro* dissolution testing. What does the word *in vitro* mean.

A. *In vitro* means we are doing it in the laboratory and nothing to do with the human body yet, but in the lab, in the laboratory.

So in the middle of this slide we have a vessel that is shown. We have some medium, some aqueous medium, in that vessel.

Q. When you say "aqueous medium," what do you mean by that?

A. It means water, for example, water or medium which has certain pHs; and then we have a tablet, that is the red tablet at the bottom of the vessel; and then we have a paddle, which basically we set it up, and if you move to the next slide, please, so here this is a typical dissolution apparatus. There

are many types of dissolution apparatuses, and this is one version. As you can see, the blue colors are the vessels. So in this particular apparatus we have about eight or seven vessels and each of them has a medium in it, medium is that water, the blue color here. There is a paddle, and you put the tablet and we set the machine, it rotates, and dissolved drug is measured automatically.

Q. You mentioned there are a couple -- there are different varieties of equipment. Can you explain to us a couple typical ones?

A. Sure. So these are just two typical apparatus, types that are used. One is vessel with a paddle in it. The other one is vessel with a basket in it. So they are referred to by *United States Pharmacopoeia*, which is a standard book that we work with. One is called apparatus one and one is two. So the one on the left-hand side is the paddle measure, or apparatus two; the one on the right-hand side is a basket measure, or apparatus one.

Q. Am I correct that on the one on the right the dosage form of the pill is inside the basket?

A. That's correct. So these are two different types, the way they operate. As you can see, on the right-hand side, the tablet is in the basket; and in the other one, tablet is at the bottom of the vessel. So these are two different apparatuses which are recognized in pharmaceutical companies.

Q. Are you familiar with the terms either "dissolution curve" or "dissolution profile"? I think the judge has heard those terms somewhat through now. Can you tell us what those terms mean?

A. Once we do the dissolution measurements, if you move to the next slide, please, so here we have on the Y axis, which is on the left side, percent of the drug which is released; and on the X axis we have time. So if you, for example, start dissolution machine and we collect data points, as shown here, so if you would go further, please.

Q. So these are points in time, a percent of drug released that's measured at a particular point in time? Is that correct?

A. That's right, yes. If you continue that until all the drug is out of the dosage form so, as you can see on the top, you can please run the curve to it, so this is how a dissolution curve is obtained, and the conditions of course have to be defined, and both condition we achieve this curve. So this is called dissolution curve.

Q. You earlier talked about immediate release dosage forms as compared to controlled release dosage forms. Is there a difference in the typical dissolution curve that you see for immediate release dosage forms as compared to the controlled release dosage forms?

A. Sure. If you would move to the next slide, please. Here

there is also animation which we pass, okay, so here is the comparison between immediate release tablets and controlled release. The red curve shows what happens with the immediate release. Practically all of the drug is dissolved within maybe 15 minutes, 30 minutes. The blue line shows the controlled release. As we can see here, slowly drug comes out over a number of hours, it could be up to 12 hours, sometimes up to 24 hours.

Q. So on the left-hand side, again, this is the amount of drug that's released, the percent of drug that's released out of the dosage form?

A. That's correct.

Q. And then as time is going on, as you move further right, that is farther in time?

A. That's right, yes.

Q. So let's then go back to the second and third steps in the process. So the absorption of the drug into the bodily tissues and then eventually into the bloodstream. Are there tests that drug developers -- or during the drug development process that are used to measure the rate and extent to which a drug is absorbed by those processes into a subject bloodstream?

A. Sure. Those are referred to as *in vivo* data. So here, if you please move to the next slide, so when we measure amount of drug in the bloodstream, how it gets there, how fast, how -- what is the duration, those kind of information that we

gathered are referred to as pharmacokinetic data or pharmacokinetic information. Basically pharmacokinetic data is used in clinical practice to ensure that drug is administered safely and effectively. It also shows the extent of drug absorption, how much drug is absorbed, how it is distributed in the body, and metabolism and as elimination.

Q. We are talking in connection with the first step, drug dissolution, there was a drug dissolution curve that we just looked at. Is there similarly a pharmacokinetic curve that is oftentimes drawn when we are dealing with the amount of drug absorbed into the bloodstream and we are talking about pharmacokinetics in the body?

A. Of course. If you would move to the next slide. So just very similar to the dissolution curve which we had *in vitro*, here this is actual curve that one gets *in vivo*, in human body. And as you can see on the Y axis is amount of drug in the blood, in the plasma or blood, and on the X axis is time. So this curve as a whole is called pharmacokinetic curve.

Q. Can you show us how this curve is developed and put together.

A. Sure. If you would move to the next slide, please. So here drug is administered to the patient or to the subject, a person, and blood samples are drawn as time goes on. So whatever is absorbed, we can take blood sample and measure. For example, this is one time point. If you move on, please,

so continue, please. So in this manner we collect blood samples and we measure how much drug is in that blood sample and we plot the curve, if you would pass the line through it. So this is a pharmacokinetic curve that we can obtain. It is called PK curve sometime.

Q. Just so we are clear here, can you describe for the court exactly what the Y axis or the horizontal --

THE COURT: Just go back to that. Let me look at the slide for a minute.

(Pause)

THE COURT: What are the two axes?

THE WITNESS: The Y axis, your Honor, to the left-hand side is -- demonstrates how much of the drug is in the blood and the other axis which shows time --

THE COURT: Time, all right.

THE WITNESS: -- is basically over what time frame, how long.

THE COURT: Okay. Very good. Go ahead.

BY MR. RHOAD:

Q. Is there a concept known as a therapeutic window in this area?

A. Yes. If you would move to the next slide, please. So in the middle of this slide you see an open wide window, which I highlighted as therapeutic window. So whenever a drug is administered, blood levels need to reach that window in order

to be effective. In other words, if a small amount of drug gets into the body, it will be too little. You may not see any effect. So therapeutic window basically is where drug concentration is going to be therapeutically effective.

If you would move to the next slide, please. So here it is an example when we have given a dosage form, but it is absorbed, but it has never reached the therapeutic window, so it is not going to be effective.

Q. And that is because not enough of the drug has gotten into the bloodstream?

A. That is correct. And if you move on to the next possibility, so if the drug gets into the bloodstream too fast, it might actually exceed the upper portion of therapeutic window, which we call it safe concentration. It goes in to gray area. Gray area usually is an area where toxicity or side effects are observed.

So ideally what we want to have, if you move to the next curve please, ideally we want absorption to happen and concentration of drug to remain in the therapeutic window as long as possible.

So one thing that controlled release dosage form do is, if they are well designed, that is what they would provide, and this is therapeutically effective and very useful.

Q. Just like we saw with dissolution curves that there was at least a somewhat typical dissolution curve for immediate

release dosage form versus the controlled release dosage forms, are there typically differences when we are looking at pharmacokinetic curves in terms of the shapes of the pharmacokinetic curves between immediate release and controlled release dosage forms?

A. Of course, just like dissolution. If you go to the next slide, please. So here, if we give it immediate release dosage form, it gets absorbed very quickly, it reaches the therapeutic window, but it also declines. So it peaks and then it goes down. If you continue administering this -- I'm sorry, if you would move to next one, yes, so here, for example, with immediate release, the problem is that we give them, they get absorbed, peak and then they go down. As they go into the yellow area, that is where there is no efficacy. That is where, if the patient is suffering from pain, during that time period which is in the yellow, that patient would suffer from pain. And, as you can see, there are peaks and troughs. In one day, for example, with immediate release, you may have to give three, four, sometimes five different dosages in order to keep blood levels in the therapeutic window.

Q. How about for a controlled release dosage form? Can you show us a typical -- do you have a slide to show us a typical pharmacokinetic curve for a controlled release product?

A. Yes. On this slide, as we have already talked about, this is a controlled release pharmacokinetic curve that we can

achieve. So here, for example, we give once-a-day dosage. And if you go on and continue on this, so if we give multiple doses every 12 hours for number of days, the advantage of controlled release is that blood levels would remain within therapeutic window. We don't have those sharp peaks and troughs. So this is in terms of therapeutic efficacy and convenience for the patient. This is what we are looking for.

Q. Are we -- in this particular slide, are we looking at PX4002.38?

A. That is correct.

Q. Is another term for pharmacokinetic curve a PK curve for short?

A. Yes, we can refer to PK curve as pharmacokinetic curve, sure.

Q. And the PK is short for pharmacokinetic?

A. Yes. PK is short for pharmacokinetics.

Q. Are there PK values or pharmacokinetic values that are oftentimes calculated in connection with studies of how much blood is absorbed into a subject's bloodstream?

A. Of course. So just if you go to the next slide, please, so here this is a pharmacokinetic curve and, as you can see, it reaches certain level, maximum concentration within therapeutic window. That concentration is referred to as C max value.

Q. Does the C max, does the C stand for something?

A. Concentration of the drug in the plasma, in the blood, as

shown also here.
Q. And how about the max, what does the max part of C max stand for?
A. Means maximum level that has reached, and C max basically, as I have put on the slide, maximum concentration of drug in bloodstream.
Q. What is the significance of the C max value when analyzing the PK data, pharmacokinetic data?
A. C max plays a major role, of course, because, first of all, we like the C max to be within therapeutic window so that it is effective. If it is in the yellow area, which I talked about, it is not effective. If it is, the C max goes in the gray area which I was talking earlier, it is going to be toxic and lots of side effects. So controlled release dosage forms provide a C max that would get there. It might not be same as immediate release. Immediate release C max is very quick. Controlled release would happen with a delayed time, but it gets there.
Q. Is there another pharmacokinetic term cited in the patent referred to as AUC?
A. Yes, there is.
Q. Can you explain to the court what AUC stands for and what it represents?
A. So we saw how drug is absorbed, and basically the pharmacokinetic curve has the measurement that we do, we measure how much is the surface area under that curve. So the

blue line is the curve, and we measure the surface area that curve covers. We call it area under the curve. So area is surface area and it represents, as I have shown on this slide, extent of absorption.

Q. So when we are talking about area, that's like if you have a rectangle, the area of the rectangle is the length times the width of the rectangle, is that right?

A. That is correct, yes.

Q. But here they are calculating using calculus and other things exactly what the area underneath of this pharmacokinetic curve is?

A. That is correct.

Q. And in the patent we see the term AUC and then a parenthetical, parentheses come after it and it says zero to INF or zero to a number. Could you explain to us what that means?

A. Sure. If you would turn to the next slide, whenever we measure area under the curve, we measure it between zero area, that is time of administration until basically an extended time frame that we call infinite. So what you see on the top of this slide is, A, you see in parenthesis you can see zero to infinity, basically means the full curve, full area under that curve. Sometimes there are different representations. For example, we can show AUC from zero to, in this case, from the slide I have, 18, it could be zero to 24. So we have that

option. But for mainly we are using entire area under the curve.

(Continued on next page)

MR. RHOAD: And just for the record, the area under the curve slide that we showed was PX4002.41, and the PK curve showing the C max value was 4002.39.

Q. Coming back then, can you tell us the significance of this PK value referred to as AUC?

A. Sure. So AUC basically shows how much of the drug has reached blood circulation. We call it extent of absorption, so that is it absorption to the full extent. So every dosages form has different strengths, and depending what strength is used, we can measure extended absorption.

Q. And the extent of the absorption, how does that relate to the significance in terms of if the patient gets the drug, what is the AUC? What is the significance of that in terms of the impact on a patient?

A. It is very significant, because the AUC shows how effective and safe the drug can be. So for example, as I showed earlier, if the AUC is too small, it is not going to be effective. If it is too large, it could be toxic. But here we have an AUC that is within the therapeutic window, so obviously therapeutic efficacy and safety of the drug is directly related to AUC.

Q. With some of that background involved about some of the background principles of controlled release dosage forms and some of the values that are measured during the process of drug delivery, let's turn to the patents in suit that we're talking about here, the '122 and the '216 patent. Could you kind of

give the Court a brief overview of exactly the nature of the '122 and '216 patents and what they teach and describe in terms of the invention?

A. Sure, if you move to next slide, please.

THE COURT: If possible, I have those patents in this binder. Is it possible that somebody has loose copies?

MR. RHOAD: We have extra copies we could hand up to Court if the Court would like.

THE COURT: I would appreciate that.

MR. RHOAD: Your Honor, we'll try to staple them so you don't lose pages.

THE COURT: All right.

MR. RHOAD: We'll have clips for you instead of stapled.

THE COURT: That's fine, very good.

BY MR. RHOAD:

Q. So you were going to give us an overview of what the '122 and '216 patents are about.

A. Sure. So I looked at the patents, and the patents are about treating pain. So in the patent they have specified in different areas, which I have highlighted here, that pain, of course, is something that we all suffer from from time to time, but there are millions of people that are chronologically in pain. And it was not addressed properly. I think earlier on Dr. Lee mentioned, and I agree, that there was problems with

treating pain. So there was a need to find something better that would help patients. So instead of giving a dosage form every four hours, there was a need to give a controlled release.

So if you move to next step, please, so controlled release formulation of oxymorphone was needed to overcome these issues.

Q. And were there --

THE COURT: I'll tell you what, sorry, I was looking down at the patent. Can you go over this slide once more, please?

THE WITNESS: Sure. This slide, your Honor, or the prior one?

THE COURT: Let's look at the prior one.

THE WITNESS: Yes. So your Honor, here the patent is talking about pain, and they do talk, for example, third line in the upper paragraph, many millions of people in the U.S. suffer from pain.

THE COURT: Now look, what is being shown here, part of the patents or what?

THE WITNESS: Yes, they are part of the specifications of the patent, your Honor. Below each box they refer to patent '122, and column one is mentioned, and lines 16 through 20 in the patent. And for example, the last paragraph shows that the schedule, rather than as needed administration of opioids, is

currently recommended the guidelines for chronic pain, and this has come from column one, lines 47 and 50 of the '122 patent.

THE COURT: I think I better take a minute and read this.

THE WITNESS: Sure.

THE COURT: Go ahead.

BY MR. RHOAD:

Q. So Dr. Fassihi, in that middle cut out from column one, lines 39 to 45, it talks about regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Do you see that?

A. Yes.

Q. What is an analgesic?

A. An analgesic is a dosage form that relieves pain.

Q. When it's talking about having regular administration to ensure that the next dose is given before the effects of the previous dose has worn off, how does that relate to your explanation before when talking about the PK curves?

A. I showed on the slide with immediate release dosage forms that they are rapidly absorbed and there are peaks and troughs. Troughs are levels of the drug in the blood that go into that yellow area that we're talking about. This one exactly. So what it means in that paragraph, in that statement in the patent, is that instead of having multiple administration, we

can give one dosage and achieve, I think we were --

Q. You want to go back to that?

Let's go back to the slide where -- this is what you were talking about the troughs and the immediate release?

A. That's right. As we can see here, the statement in the patent talks about regular administration, so that before the pain comes back, we give another dose. So very inconvenient, multiple administration, three, four, five times a day to treat pain. So that is what they talked about.

Q. When it's talking about regular administration, so you give it before the next dose wears off, how does that relate to the controlled release curve that we looked at earlier?

A. If you go to that curve, if you would, please, so controlled release, as we can see here, the drug remains in the therapeutic window, and we only give it once a day, that is every twelve hours or sometimes twice a day, basically.

Q. Twelve hours, is that twice a day?

A. Well, every twelve hours, twice a day. So the blood levels remain in the therapeutic window and the patient is -- mainly the pain is not there any more.

Q. If we go back to the slide, which is PX 4002.45 where we were looking at some of the statements in the patent.

A. Yes. So if you would go to the next step, please.

So based on this -- so this is a different excerpt from the patent '122.

Q. Are these all still from column one? These are three different excerpts from column one of the '122 patent, is that right?
A. That is correct.
Q. And the same language also appears in the '216 patent, is that right?
A. That is right, yes. So here the top one talks about oxymorphone, which is marketed as an injection. It is also available as a suppository.
Q. So an injection is then something that is injected directly into the bloodstream, it's not taken orally, is that right?
A. That is correct. So this is what was available regarding oxymorphone.
Q. At the time the patents were filed?
A. That is correct. So there was also at one time the immediate release dosage form that was used, but it was taken off market for some reason. And we knew that there was a need for pain prevention, so controlled release formulation was something that the inventors of the patent came up with. So they developed this formulation so that it can be used on a daily basis to prevent pain.
Q. What do we see on this next slide again. Are these all excerpts from column two? This is on slide PX 4002.47. Are these all excerpts from column two of the '122 patent?
A. That's correct.

Q. And this language appears as well in the '216 patent?
A. Yes, it does. And again we read here on this slide it talks about drug metabolism and so on.
Q. And the drug metabolism, that's what you were talking about what happens in the liver as part of that third step in the process, is that right?
A. That's correct. In the middle section of this slide it talks about oxymorphone is metabolized basically in the liver resulting in an oral bioavailability of about ten percent.
Q. That was the oral bioavailability where you showed the ten percent and then the 60 percent. If we can go to the slide that showed that.

Well --

A. Yes, the slide that --
Q. Sorry here we are. Thank you.

So if we can go -- this is the slide where you were talking about bioavailability. So oxymorphone has a bioavailability as reported in the patent of ten percent, like in the orange on PX 4002.16, is that right?
A. That is correct, yes.

Basically there was a need for controlled release formulation. The patients needed that, but no one really thought of using oxymorphone except the inventors of the patents.
Q. And so what is the -- what is it that the patentees

invented as described in the patent?
A. Well, the summary of the invention -- and I read that from the slide -- this invention provides methods of relieving pain by administering the controlled release pharmaceutical tablet which contains oxymorphone which produces at least predetermined minimum blood plasma levels for at least twelve hours after dosing with tablets that produce the sustained pain relief over time period.
Q. And can you describe for the Court at a sort of high level what the nature of the invention is that is taught in claim --
Before we get there, let's look, is there PK curves, the curves that show the amount of drug that gets into the bloodstream that are reported in the patent?
A. Yes, this is figure five from '122 patent. And here in this figure, which these are excerpts from figure five that are presented here, so we have an immediate release oxymorphone which is administered to a subject, to a human subject, and you can see how fast it is absorbed. It peaks and then rapidly comes down.
Q. And immediate release is denoted there IR in the red, is that right?
A. Right. IR stands for immediate release.
And the blue curve is a controlled release oxymorphone formulation that was administered. And as you can see, absorption is much slower. The peaks are much lower. In other

words, this is where the therapeutic window was that I was talking about. So these peaks, these blood levels that we see for the blue CR stands for controlled release. So this is a typical curve for controlled release here in this figure and shows the differences between IR versus CR.

Q. Does the patent also include figures that relate to pain relief that was seen by subjects who received a dose of the controlled release oxymorphone tablets described in the patents?

A. Sure. If you would move to next slide, here this is a figure two from the '122 as well as '216 patent. And if you look at the highlighted yellow curve and values which are mentioned, on the Y axis we have pain intensity differences or basically supression of pain. So the curve, as we can see, is arrived from patients that were given oxymorphone and the pain was measured. So this curve shows that over time, over a two-hour period after that administration of the oxymorphone tablet, the pain was controlled, it was suppressed, as you can see the curve is continuously coming down. So that shows that the pain relief is there.

THE COURT: All right. Tomorrow we'll start at 11:30, please, 11:30.

(Adjourned to March 27, 2015 at 11:30 a.m.)

INDEX OF EXAMINATION

DEFENDANT EXHIBITS